IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant: | David J. Grainger et al. | Examiner: | Umamaheswari Ramachandran |
| Serial No.: | 10/729,056 | Group Art Unit: | 1617 |
| Filed: | December 5, 2003 | Docket No.: | 295.009US4 |
| Customer No.: | 21186 | Confirmation No.: | 9616 |
| Title: | PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES | | |

## DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dr. David J. Grainger, declare and say as follows:

1. I am one of the named co-inventors of the claims of the present application. I make this Declaration in support of the patentability of the claims of the above-identified application.

2. The present application is a continuation of U.S. application Serial No. 09/754,775, filed January 4, 2001 which is a continuation application of U.S. application Serial No. 08/973,570, filed December 5, 1997, which is a national stage filing of PCT/US96/10211, filed June 7, 1996, which is a continuation-in-part of U.S. application Serial No. 08/478,936, filed June 7, 1995, abandoned; U.S. application 08/476,735, filed June 7, 1995, now U.S. Patent No. 5,595,722; U.S. application Serial No. 08/477,393, filed June 7, 1995, pending; and U.S. application Serial No. 08/486,334, filed June 7, 1995, now U.S. Patent No. 5,770,609, which is a continuation-in-part of U.S. application 08/242,161, filed May 12, 1994, which is a continuation-in-part of U.S. application 08/061,714, filed May 13, 1993.

3. In the Office Action dated March 20, 2009, the Examiner rejected claims 153-154, 157-158, 160-163, 165, 169-173, and 181-182 under 35 U.S.C. § 102(e) as being anticipated by Black et al. (U.S. Patent No. 5,464,845); claims 153-154, 157-158, 160-163, 165, 169-177, and 181-182 under 35 U.S.C. § 102(e) as being anticipated by

Sall (U.S. Patent No. 5,441,965); claim 159 under 35 U.S.C. § 103(a) as being unpatentable over Black et al.; claim 159 under 35 U.S.C. § 103(a) as being unpatentable over Sall; claim 164 under 35 U.S.C. § 103(a) as being unpatentable over Black et al. in view of Cullinan et al. (U.S. Patent No. 5,457,113); claim 164 under 35 U.S.C. § 103(a) as being unpatentable over Sall; claims 174-177 under 35 U.S.C. § 103(a) as being unpatentable over Black et al. in view of Sall; and claims 179 and 180 under 35 U.S.C. § 103(a) as being unpatentable over Sall in view of Willson (U.S. Patent No. 5,681,835).

4. Prior to the effective filing date of the present application, i.e., May 13, 1993, compounds that were considered to be analogs of tamoxifen were also considered to be anti-estrogens. For instance, prior to the effective filing date of the present application, compounds with structural relatedness to tamoxifen were believed to elicit a beneficial effect as a result of their anti-estrogenic activity. As such, it was understood that the target for those compounds was the estrogen receptor.

5. U.S. application Serial No. 08/061,714, the parent application of the above-referenced application, discloses that TGF-beta activators and TGF-beta production stimulators, such as tamoxifen and analogs thereof, may be employed to prevent or treat conditions characterized by inappropriate proliferation of smooth muscle cells, such as restenosis or other vascular trauma, following graft or transplant. It is also disclosed that TGF-beta activators and TGF-beta production stimulators may be employed to prevent or treat disease states including thrombosis, myocardial infarction, stroke and atherosclerosis, e.g., by reducing, delaying or eliminating atherosclerotic plaque. The '714 application discloses that tamoxifen increased TGF-beta1 RNA in rat vascular smooth muscle cells.

6. Raloxifene shares some structural attributes with tamoxifen. The Black et al. and Sall patents disclose the use of raloxifene and analogs thereof.

7. Although raloxifene may have some structural relationship to tamoxifen, it does not elevate TGF-beta1 levels. Yang and colleagues showed that raloxifene increases TGF-beta3 expression, but does not affect TGF-beta1 levels in cell culture (see Figure 2 of Yang et al., Endocrinology, 137:2075 (1996)). Similarly, Ozmen et al., Eur Cytokine Network, 18:148 (2007) and Kumru et al., Arch. Gynecol. Obstet., 277:489 (2008) both found no change in TGF-beta1 levels in women treated with raloxifene. Furthermore, Dixon et al., Am. J. Nephrol., 27:120 (2007) actually reported a decrease in TGF-beta1 following raloxifene treatment in rats

8. Thus, the anti-estrogenic activity of compounds, such as those with some structural relationship to tamoxifen, is independent of TGF-beta elevating activity. It is not therefore possible to infer the likely beneficial properties of compounds structurally related to tamoxifen by selecting a single example (in this case raloxifene) which shares the anti-estrogenic properties of tamoxifen but not the TGF-beta1 elevating properties disclosed in the present application.

9. Furthermore, any inference that raloxifene might have been predicted to have the beneficial properties of the compounds recited in the claims of the application, has been shown to be incorrect: raloxifene (which is anti-estrogenic but does not elevate TGF-beta1) does not prevent cardiovascular disease in humans (Barrett-Connor et al., New England J. Med., 355:125 (2006)), while tamoxifen (which is a less powerful anti-estrogen but does elevate TGF-beta1) does prevent cardiovascular disease in humans (Braithwaite et al., J. Gen. Intern Med., 18:937 (2003)).

10. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 14th JULY 2009 By

Dr. David J. Grainger